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Date: March 17, 2004 **File Number: 9233-62**

Telecopier No.: 703-872-9306 **Telephone No.:**

To: **Jeffrey E. Russel**

Company: **U.S. Patent and Trademark Office, GAU 1654**

From: **Shawna Cannon Lemon**

Number of Pages: 12 **Return fax to: sef**

If there is a problem with this transmission, please call (919) 854-1400. Our fax number is (919) 854-1401.

Examiner Russel: Per your request, attached is the October 14, 2003 Office Action for USSN 09/873,757, including document included therewith.

SCL

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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/873,757	06/04/2001	Nnochiri N. Ekwuribe	9233-62	2357

20792 7590 10/14/2003

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EXAMINER	
RUSSEL, JEFFREY E	

ART UNIT	PAPER NUMBER
1654	

DATE MAILED: 10/14/2003

Please find below and/or attached an Office communication concerning this application or proceeding.

PTO-90C (Rev. 10/03)

Office Action Summary	Application No.	Applicant(s)	
	09/873,757	EKWURIBE ET AL.	
	Examiner	Art Unit	
	Jeffrey E. Russel	1654	

-- *The MAILING DATE of this communication appears on the cover sheet with the correspondence address* --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *26 August 2003* .

2a)☒ This action is FINAL. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-8,10-19,21-44,46-49 and 51-102* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-8,10-19,21-44,46-49,51-67,70,71,75,76,80,81,86-92,95,96,100 and 101* is/are rejected.

7)☒ Claim(s) *68,69,72-74,77-79,82-85,93,94,97-99 and 102* is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *26 August 2003* is/are: a)☒ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12)☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a) ☐ The translation of the foreign language provisional application has been received.

15)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449) Paper No(s) *0803* .
4) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other:

1. Claims 88-92 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. There is no antecedent basis in the claims for the phrase "the lipophilic moiety" in claims 88-92. Note that independent claim 40 is directed to mixtures of conjugates comprising polypropylene glycol rather than lipophilic moieties.

2. Claims 97 and 102 are objected to because of the following informalities: Claims 97 and 102 are identical in scope. It is believed that claim 97 should instead depend upon claim 42. Appropriate correction is required.

3. The nonstatutory double patenting rejection is based on a judicially created doctrine grounded in public policy (a policy reflected in the statute) so as to prevent the unjustified or improper timewise extension of the "right to exclude" granted by a patent and to prevent possible harassment by multiple assignees. See *In re Goodman*, 11 F.3d 1046, 29 USPQ2d 2010 (Fed. Cir. 1993); *In re Longi*, 759 F.2d 887, 225 USPQ 645 (Fed. Cir. 1985); *In re Van Ornum*, 686 F.2d 937, 214 USPQ 761 (CCPA 1982); *In re Vogel*, 422 F.2d 438, 164 USPQ 619 (CCPA 1970);and, *In re Thorington*, 418 F.2d 528, 163 USPQ 644 (CCPA 1969).

A timely filed terminal disclaimer in compliance with 37 CFR 1.321(c) may be used to overcome an actual or provisional rejection based on a nonstatutory double patenting ground provided the conflicting application or patent is shown to be commonly owned with this application. See 37 CFR 1.130(b).

Effective January 1, 1994, a registered attorney or agent of record may sign a terminal disclaimer. A terminal disclaimer signed by the assignee must fully comply with 37 CFR 3.73(b).

4. Claims 1-8, 10-19, 21-44, 46-49, and 51-67 are provisionally rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 1-103 of copending Application No. 09/873,797. Although the conflicting claims are not identical, they are not patentably distinct from each other. Note that the '797 application claims purely monodispersed mixtures of a drug coupled to a polyalkylene glycol moiety (see, e.g., claim 1) where the drug can be growth hormone peptides (see, e.g., claim 64) and the polyalkylene glycol moiety can be polyethylene glycol or polypropylene glycol (see, e.g., claims 21 and 23) and

where a lipophilic moiety can be present in the conjugates (see, e.g., claim 9), and that the '797 application claims forming these conjugates (see, e.g., claims 95-102) by the same method claimed in the instant application. While the '797 application does not claim human growth hormone as a source of the growth hormone to be conjugated, it would have been obvious to one of ordinary skill in the art to use human growth hormone as the source of the growth hormone in the claimed invention of the '797 application because human growth hormone is a known source of therapeutic growth hormone, and because conjugation of human growth hormone according to the claimed invention of the '797 application would have been expected to increase the human growth hormone's resistance to in vivo proteolysis and to increase its in vivo have-life. With respect to claims 28 and 29, while the '797 application does not claim the use of its growth hormone conjugates to treat growth hormone deficiency or to accelerate the growth rate of an animal, it would have been obvious to one of ordinary skill in the art to use the growth hormone conjugates of the '797 application to treat growth hormone deficiency or to accelerate the growth rate of an animal, because these are common uses for growth hormone and because it is routine to use conjugated protein or peptide therapeutics to treat diseases which are known in the art to be treatable with the unconjugated protein or peptide.

This is a provisional obviousness-type double patenting rejection because the conflicting claims have not in fact been patented.

5. Claims 59-67 are provisionally rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 1-41 of copending Application No. 09/873,731 in view of Clark (U.S. Patent No. 5,597,797) or Cunningham et al (U.S. Patent No. 6,057,292). Although the conflicting claims are not identical, they are not

patentably distinct from each other. The '731 application claims the same method steps as are recited in the instant claims for forming the substantially monodispersed mixture of polymers having the structure of Formula III, but does not claim then activating the polymers and reacting them with growth hormone in order to form growth hormone conjugates. Clark teaches forming PEG-human growth hormone conjugates by first activating the PEG and then reacting the activated PEG with the human growth hormone, preferably with the epsilon-amino group of a lysine residue (see, e.g., column 5, lines 45-57; column 10, lines 50-56; and column 13, lines 34-39). Cunningham et al teach forming PEG-human growth hormone conjugates by first activating the PEG and then reacting the activated PEG with the human growth hormone, preferably with the epsilon-amino group of a lysine residue (see, e.g., column 20, line 53 - column 21, line 67; column 23, lines 45-55; and column 25, lines 11-39). It would have been obvious to one of ordinary skill in the art to use the claimed method of the '731 application as a source of the PEG used in Clark's method or Cunningham et al's method for forming PEG-human growth hormone conjugates because it is prima facie obvious to use the product of one process as the source of reactant for another process (see In re Kamlet, 88 USPQ 106 (CCPA 1950)).

This is a provisional obviousness-type double patenting rejection because the conflicting claims have not in fact been patented.

6. The text of those sections of Title 35, U.S. Code not included in this action can be found in a prior Office action.

7. Claims 1-6, 10, 11, 16-19, 21-23, 26-38, 42-44, 48, 49, 53, 54, 58, 70, 71, 75, 76, 80, 81, 86, 87, 95, 96, 100, and 101 are rejected under 35 U.S.C. 103(a) as being obvious over Ekwuribe (U.S. Patent No. 5,359,030) in view of Delgado et al (U.S. Patent No. 5,349,052), the WO Patent

Application 97/14740, Clark (U.S. Patent No. 5,597,797), and Cunningham et al (U.S. Patent No. 6,057,292). Ekwuribe teaches conjugates in which a polymer comprising a PEG moiety which preferably has more than 7 subunits and a lipophilic moiety which can be a fatty acid such as lauric, palmitic, oleic, or stearic acid are conjugated via a labile bond to a peptide, which can be somatotropin (i.e. growth hormone) and which conjugation can occur at an amine group present on the peptide. Plural polymers can be conjugated to each peptide. Conjugation results in prolonged blood circulation and enhanced resistance to enzymatic degradation, relative to the peptide alone. See, e.g., the Abstract; column 6, lines 41-61; column 11, line 20; column 12, lines 11-16 and 35-40; column 13, Conjugates 2 and 3; column 14, lines 3-14 and 43-55; and claim 19. Ekwuribe does not teach monodispersed conjugate mixtures with low molecular weight distribution standard deviations and high dispersity coefficients. Delgado et al disclose the desirability of optimizing PEG length and degree of substitution and of fractionating protein-PEG conjugates in order to isolate the specific conjugate possessing optimal biological properties. See, e.g., the Abstract; column 6, lines 19-41; and claims 1-9. The WO Patent Application 97/14740 discloses the desirability of preparing polyethylene glycols of discrete length for the purpose of preparing protein conjugates which have uniform properties and reduced immunogenicity. See, e.g., page 2, lines 3-13; page 4, lines 3-29; page 5, line 31 - page 6, line 7; and page 11, lines 8-12. It would have been obvious to one of ordinary skill in the art at the time Applicant's invention was made to prepare the somatotropin conjugates of Ekwuribe using the discrete length PEG of the WO Patent Application '740 and to purify the resulting conjugates according to the method of Delgado et al because it is prima facie obvious to use any available source of a reactant (see In re Kamlet, 88 USPQ 106 (CCPA 1950)), and the method of

the WO Patent Application '740 is an available source of the PEG required by Ekwuribe; because the use of discrete length PEG in the conjugates of Ekwuribe would have been expected to have the benefit of producing a product with uniform properties and reduced immunogenicity as taught by the WO Patent Application '740; and because purifying the PEG conjugate according to the method of Delgado would have been expected to have the benefit of being able to isolate the specific conjugate having the most desirable biological properties. Ekwuribe does not teach using human somatotropin as the source of the somatotropin for its conjugates, and does not teach conjugation at the amino groups present in the human somatotropin. Clark teaches conjugating polyethylene glycol molecules preferably to epsilon-amino groups of lysine residues present in human growth hormone. See, e.g., column 5, lines 45-57; column 10, lines 11-56; and column 13, lines 34-39. Cunningham et al teach conjugating polyethylene glycol molecules to epsilon-amino groups of lysine residues present in human growth hormone. See, e.g., column 20, line 53 - column 21, line 54; column 23, lines 45-55; column 25, lines 11-39; and column 27, lines 2-20. It would have been obvious to one of ordinary skill in the art at the time Applicants' invention was made to use human somatotropin as the source of the somatotropin for the conjugates of Ekwuribe because Clark and Cunningham et al et al teach that human growth hormone is an effective source of somatotropin in making such conjugates and because human somatotropin possesses therapeutic properties which would have been expected to have been useful in the conjugates of Ekwuribe. It would have been obvious to one of ordinary skill in the art at the time Applicants' invention was made to conjugate the polymers of Ekwuribe to the sidechains of the Lys residues present in human somatotropin because Clark and Cunningham et al disclose that these residues are useful attachment points for forming

somatotropin conjugates. Ekwuribe does not teach using somatotropin-based conjugates to treat growth hormone deficiency or to accelerate the growth of animals. Cunningham et al teach polyethylene glycol conjugated to human growth hormone and used to treat growth hormone deficiency and to accelerate the growth of animals. See, e.g., column 20, line 53 - column 21, line 54; column 23, lines 45-55; column 25, lines 11-39; and column 27, lines 2-20. It would have been obvious to one of ordinary skill in the art at the time Applicant's invention was made to use the somatotropin-based conjugates of Ekwuribe for the above-recited purposes because the treatment of growth hormone deficiency and the acceleration of the growth rate of animals are primary uses of somatotropin conjugates as shown by Cunningham et al.

8. Claim 12 is rejected under 35 U.S.C. 103(a) as being obvious over Ekwuribe (U.S. Patent No. 5,359,030) in view of Delgado et al (U.S. Patent No. 5,349,052), the WO Patent Application 97/14740, Clark (U.S. Patent No. 5,597,797), and Cunningham et al (U.S. Patent No. 6,057,292) as applied against claims 1-6, 10, 11, 16-19, 21-23, 26-38, 42-44, 48, 49, 53, 54, 58, 70, 71, 75, 76, 80, 81, 86, 87, 95, 96, 100, and 101 above, and further in view of the Harris et al article (J. Macromol., Sci., Vol. C25, pages 325-373). Ekwuribe does not teach the number or the size of the oligomers which are to be conjugated to each somatotropin molecule. The Harris et al article teaches that when using PEG-protein conjugates, the degree of substitution and PEG molecular weight should be optimized in order to achieve the protein's desired effect (see, e.g., page 351, first full paragraph). Accordingly, it would have been obvious to one of ordinary skill in the art at the time Applicant's invention was made to optimize result-effective conjugate properties, e.g., degree of substitution and polymer size, as taught by the Harris et al article for the PEG-somatotropin conjugates of Ekwuribe in order to maximize the conjugates' desirable properties.

9. Applicant's arguments filed August 26, 2003 have been fully considered but they are not persuasive.

Because this application is not yet in condition for allowance, the provisional obviousness-type double patenting rejections have been maintained.

The obviousness rejection based upon Ekwuribe (U.S. Patent No. 5,359,030) as the primary reference is maintained. In the arguments, Applicants stated that the rejection set forth in paragraph 13 of the first Office action is overcome by the lipophilic moiety limitation, and that the rejection set forth in paragraph 12 of the first Office action is overcome by the human growth hormone limitation. However, this argument overlooks the fact that the rejection set forth in paragraph 13 of the first Office action referred back to the rejection in paragraph 12 (note the phrase "as applied against claims 1-6, 16-23, 26-38, 42-44, 48, 49, 53, 54, and 58 above" in the rejection in paragraph 13). While Applicants' amendments require that the two rejections set forth in the first Office action be combined into a single rejection in this Office action, they do not avoid the examiner's argument that Ekwuribe suggests the presence of a lipophilic moiety and that Clark and Cunningham et al suggest the use of human growth hormone.

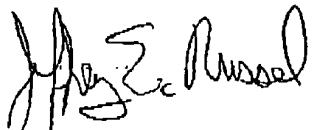
10. Claims 68, 69, 72-74, 77-79, 82-85, 93, 94, 98, and 99 are objected to as being dependent upon a rejected base claim, but would be allowable if rewritten in independent form including all of the limitations of the base claim and any intervening claims. Claims 97 and 102 would be allowable if rewritten to overcome the claim objections set forth in this Office action and to include all of the limitations of the base claim and any intervening claims. With respect to these claims, Ekwuribe does not teach or suggest a lipophilic moiety which is an alkyl moiety or which is a fatty acid moiety having 4-6 carbon atoms.

11. Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL.** See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Jeffrey E. Russel at telephone number (703) 308-3975. The examiner can normally be reached on Monday-Thursday from 8:30 A.M. to 6:00 P.M. The examiner can also be reached on alternate Fridays.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor Brenda Brumback can be reached at (703) 306-3220. The fax number for Art Unit 1654 for formal communications is (703) 305-3014; for informal communications such as proposed amendments, the fax number (703) 746-5175 can be used. The telephone number for the Technology Center 1 receptionist is (703) 308-0196.



Jeffrey E. Russel
Primary Patent Examiner
Art Unit 1654

JRussel
October 10, 2003

Substitute form 1449A/PTO

INFORMATION DISCLOSURE STATEMENT BY APPLICANT

(use as many sheets as necessary)

Sheet 1 of 1

Complete if Known	
Application Number	09/873,757
Filing Date	06/04/2001
First Named Inventor	Nnochiri N. Ekwuribe
Group Art Unit	1654
Examiner Name	J. Russel
Attorney Docket Number	9233-62

U.S. PATENTS AND PATENT PUBLICATIONS Class/Subclass

Examiner Initials*	Cite No.	U.S. Patent Document Number	Kind Code (if known)	Name of Patentee or Applicant of Cited Document	Date of Publication of Cited Document MM-DD-YYYY	Pages, Columns, Lines, Where Relevant Passages or Relevant Figures Appear
JRL	1	2003/0144468	A1	Ekwuribe et al.	07/31/2003	528/425
JRL	2	2003/0087808	A1	Soltero et al.	05/08/2003	514/3
JRL	3	2003/0083232	A1	Soltero et al.	05/01/2003	514/3
JRL	4	2003/0069170	A1	Soltero et al.	04/10/2003	514/2.
JRL	5	2003/0060606	A1	Ekwuribe et al.	03/27/2003	530/399
JRL	6	2003/0050228	A1	Ekwuribe et al.	03/13/2003	514/3
JRL	7	2003/0027748	A1	Ekwuribe et al.	02/06/2003	514/3
JRL	8	2003/0004304	A1	Ekwuribe et al.	01/02/2003	

FOREIGN PATENT DOCUMENTS

Examiner Initials*	Cite No.	Foreign Patent Document Office	Number	Kind Code (if known)	Name of Patentee or Applicant of Cited Document	Date of Publication of Cited Document MM-DD-YYYY	Pages, Columns, Lines, Where Relevant Passages or Relevant Figures Appear	T

OTHER NON PATENT LITERATURE DOCUMENTS

Examiner Initials*	Cite No.	Include name of the author (in CAPITAL LETTERS), title of the article (when appropriate), title of the item (book, magazine, journal, serial, symposium, catalog, etc.), date, page(s), volume-issue number(s), publisher, city and/or country where published	T
JRL	9	Still et al., *Methods of Reducing Hypoglycemic Episodes in the Treatment of Diabetes Mellitus*, U.S. Serial No. 10/461,199, filed 06/13/2003	
JRL	10	Radhakrishnan et al., *Insulin Polypeptide-Oligomer Conjugates, Proinsulin Polypeptide-Oligomer Conjugates and Methods of Synthesizing Same*, U.S. Serial No. 10/389,499, filed 03/17/2003	
JRL	11	Soltero et al., *Pharmaceutical Compositions of Insulin Drug-Oligomer Conjugates and Methods of Treating Diseases Therewith*, U.S. Serial No. 10/382,155, filed 03/05/2003	
JRL	12	Soltero et al., *Pharmaceutical Compositions of Drug-Oligomer Conjugates and Methods of Treating Diseases Therewith*, U.S. Serial No. 10/382,069, filed 03/05/2003	
JRL	13	Soltero et al., *Insulin Polypeptide-Oligomer Conjugates, Proinsulin Polypeptide-Oligomer Conjugates and Methods of Synthesizing Same*, U.S. Serial No. 10/382,022, filed 03/05/2003	
JRL	14	Ekwuribe et al., *Calcitonin Drug-Oligomer Conjugates, and Uses Thereof*, U.S. Serial No. 10/166,355, filed 11/08/2002, including Preliminary Amendment dated 02/26/2003 and Supplemental Preliminary Amendment dated 03/31/2003	
JRL	15	Ekwuribe et al., *Mixtures of Drug-Oligomer Conjugates Comprising Polyalkylene Glycol, Uses Thereof, and Methods of Making Same*, U.S. Serial No. 09/873,797, filed 06/04/2001	

Examiner Signature	Jeffrey G. Russe	Date Considered	October 10, 2003

*EXAMINER: Initial if reference considered, whether or not citation is in conformance with MPEP 609. Draw line through citation if not in conformance and not considered. Include copy of this form with next communication to applicant.